CLAIMS

1. A method for maintaining the quality of aqueous injection preparation of thrombomodulin in a non-frozen or non-freeze-dried liquid form over its storage and transportation, characterized in that the aqueous injection preparation of thrombomodulin is prepared as an aqueous solution having a pH value in the range from 5 to 7.0 and containing a soluble thrombomodulin in an effective amount and buffer component(s) revealing a buffering action in a pH range between 5 and 7.0, wherein the aqueous solution of thrombomodulin has either the following characteristic feature a) or b), namely,

a) that it contains further a surfactant and is filled aseptically in a container or

b) that it consists of a prefilled syringe preparation filled aseptically in a syringe container so as to exclude any substantial gas space therein.

2. The method as claimed in claim 1, wherein the aqueous injection preparation of thrombomodulin, which is characterised in that it is prepared as an aqueous solution having a pH value in the range from 5 to 7.0 and containing (a) soluble thrombomodulin in an effective amount, buffer component(s) revealing a buffering action in a pH range between 5 and 7.0 and a surfactant and is filled in a container aseptically, is stored/transported in a liquid form over a long period of time.

3. The method as claimed in claim 1, wherein the

aqueous injection preparation of thrombomodulin, which is characterised in that it is prepared as an aqueous solution having a pH value in the range from 5 to 7.0 and containing a soluble thrombomodulin in an effective amount and buffer component(s) revealing a buffering action in a pH range between 5 and 7.0 and consists of a prefilled syringe preparation filled aseptically in a syringe container so as to exclude any substantial gas space therein, is stored/transported in a liquid form over a long period of time.

4. The method as claimed in ~~any one of claims 1 to 3~~ claim 1, wherein the aqueous injection preparation of thrombomodulin, which is characterised in that it is prepared as an aqueous solution having a pH value in the range from 5 to 7.0 and containing a soluble thrombomodulin in an effective amount, buffer component(s) revealing a buffering action in a pH range between 5 and 7.0 and a surfactant and consists of a prefilled syringe preparation filled aseptically in a syringe container so as to exclude any substantial gas space therein, is stored/transported in a liquid form over a long period of time.

5. The method as claimed in ~~any one of claims 1 to 4~~ claim 1, wherein the soluble thrombomodulin is a peptide which is characterized in that it has a molecular weight of 66,000 ± 10,000, as determined by an SDS-polyacrylamide gel electrophoresis in non-reduced state, exhibits a function for accelerating the activation of protein C by thrombin and is soluble in water for injection at least at a concentration of 6 mg/ml.

6. The method as claimed in ~~any one of claims 1 to 5~~ claim 1, wherein the soluble thrombomodulin exhibits the function for accelerating the activation of protein C by thrombin and consists of either the following i) or ii), namely,

i) a thrombomodulin which is constituted of an amino acid sequence composed of the amino acid residues from the 19th site to the 516th site of the sequence listing SEQ ID NO: 1 or

ii) a thrombomodulin which is constituted of an amino acid sequence composed of those amino acid residues in which one or more amino acid resudues in the amino acid sequence given above are replaced or removed or one or more amino acid residues are added thereto.

7. The method as claimed in ~~any one of claims 1 to 6~~ claim 1, wherein the soluble thrombomodulin is any one among the group consisting of that constituted of the amino acid sequence composed of the amino acid residues from the 19th site to the 516th site of the sequence listing SEQ ID NO: 1, that constituted of the amino acid sequence composed of the amino acid residues from the 19th site to the 516th site of the sequence listing SEQ ID NO: 2, that obtained by transfecting the DNA segment coding the amino acid sequence given in the sequence listing SEQ ID NO: 1 to a host cell and that obtained by transfecting the DNA segment coding the amino acid sequence given in the sequence listing SEQ ID NO: 2 to a host cell.

8. Th method as claimed in ~~any one of claims 1~~ claim 1

~~to 7~~, wherein the buffer component consists of at least one among buffer components based on phosphate and acetate.

9. The method as claimed in ~~any one of claims 1 to 8~~ claim 1, wherein the pH value of the aqueous solution is in the range from 5.5 to 6.5.

10. The method as claimed in ~~any one of claims 1 and 3 to 9~~ claim 1, wherein the prefilled syringe preparation, which is filled aseptically in the syringe container so as to exclude any substantial gas space therein, is characterized in that the aqueous solution of thrombomodulin occupies the syringe container in such an amount that the residual gas space therein does not exceed 15 % by volume in terms of the proportion of gas space.

11. The method as claimed in any one of claims 1 and 3 to 10, wherein the inner diameter of the syringe container for the prefilled syringe preparation is 8.6 mm or less.

12. An aqueous injection preparation of thrombomodulin in a non-frozen or non-freeze-dried liquid form, superior in the stability for long term storage and in the stability against shaking and suitable for storing/transporting over a long period of time, characterized in that the aqueous injection preparation of thrombomodulin has a pH value in the range from 5 to 7.0, contains a soluble thrombomodulin in an effective amount, buffer component(s) revealing a buffering action in a pH range between 5 and 7.0 and a surfactant and is filled in a container aseptically.

13. An aqueous injection preparation of thrombomodulin in a non-frozen or non-freeze-dried liquid form, superior in the stability for long term storage and in the stability against shaking and suitable for storing/transporting over a long period of time, characterized in that the aqueous injection preparation of thrombomodulin is a prefilled syringe preparation which has a pH value in the range from 5 to 7.0, contains a soluble thrombomodulin in an effective amount and buffer component(s) revealing a buffering action in a pH range between 5 and 7.0 and which is filled in a syringe container aseptically so as to exclude any substantial gas space therein.

14. An aqueous injection preparation of thrombomodulin in a non-frozen or non-freeze-dried liquid form, superior in the stability for long term storage and in the stability against shaking and suitable for storing/transporting over a long period of time, characterized in that the aqueous injection preparation of thrombomodulin is a prefilled syringe preparation which has a pH value in the range from 5 to 7.0, contains a soluble thrombomodulin in an effective amount, buffer component(s) revealing a buffering action in a pH range between 5 and 7.0 and a surfactant and which is filled in a syringe container aseptically so as to exclude any substantial gas space therein.

15. An aqueous injection preparation of thrombomodulin as claimed in claim 13 ~~or 14~~, wherein the prefilled syringe preparation is for subcutaneous injection or for intramuscular injection.

16. An aqueous injection preparation of thrombomodulin as claimed in ~~any one of claims 12 to 15~~ claim 12, wherein the soluble thrombomodulin is any one among the group consisting of that constituted of the amino acid sequence composed of the amino acid residues from the 19th site to the 516th site of the sequence listing SEQ ID NO: 1, that constisuted of the amino acid sequence composed of the amino acid residues from the 19th site to the 516th site of the sequence listing SEQ ID NO: 2, that obtained by transfecting the DNA segment coding the amino acid sequence given in the sequence listing SEQ ID NO: 1 to a host cell and that obtained by transfecting the DNA segment coding the amino acid sequence given in the sequence listing SEQ ID NO: 2 to a host cell.

17. An aqueous injection preparation of thrombomodulin as claimed in ~~any one of claims 12 to 16~~ claim 12, wherein the pH of the buffur solution is in the range from 5.5 to 6.5.

18. An aqueous injection preparation of thrombomodulin as claimed in ~~any one of claims 13 to 17~~ claim 13, wherein the prefilled syringe preparation, which is filled aseptically in the syringe container so as to exclude any substantial gas space therein, is characterized in that the aqueous solution of thrombomodulin occupies the syringe vessel in such an amount that the residual gas space therein does not exceed 15 % by volume in terms of the proportion of gas space.

19. An aqueous injection preparation of

thrombomodulin as claimed in claim 13 ~~any one of claims 13 to 18~~, wherein the inner diameter of the syringe container for the prefilled syringe preparation is 8.6 mm or less.

20. A method for maintaining the concentration of a soluble thrombomodulin in blood, characterized in that an aqueous injection preparation of thrombomodulin is used, which preparation contains an effective amount of a soluble thrombomodulin exhibiting a sustained effectiveness to be administered to the patient by subcutaneous or intramuscular injection at an administration frequency of once per 2 to 5 days.

21. A method as claimed in claim 20, wherein the soluble thrombomodulin is any one among the group consisting of that constituted of the amino acid sequence composed of the amino acid residues from the 19th site to the 516th site of the sequence listing SEQ ID NO: 1, that constituted of the amino acid sequence composed of the amino acid residues from the 19th site to the 516th site of the sequence listing SEQ ID NO: 2, that obtained by transfecting the DNA segment coding the amino acid sequence given in the sequence listing SEQ ID NO: 1 to a host cell and that obtained by transfecting the DNA segment coding the amino acid sequence given in the sequence listing SEQ ID NO: 2 to a host cell.